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Title of Study:

Drug-Eluting Bead, Irinotecan Therapy of Unresectable Intrahepatic Cholangiocarcinoma (DELTIC) with Concomitant Systemic Gemcitabine and Cisplatin or Carboplatin

Date Issued: 3/30/2017

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Investigational Plan & Clinical Study Protocol

Drug-**EL**uting Bead, Irinotecan **T**herapy of Unresectable **I**ntrahepatic **C**holangiocarcinoma (**DELTIC**) with Concomitant Systemic Gemcitabine and Cisplatin or Carboplatin

PROTOCOL #: UL 2011.1

Date Issued: March 30, 2017

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1 Protocol Synopsis

1.1 Title	Drug-Eluting Bead, Irinotecan (DEBIRI) Therapy of Unresectable intrahepatic cholangiocarcinoma (ICC) with Concomitant Systemic Gemcitabine and Cisplatin (Gem-Cis) or Gemcitabine and Carboplatin (Gem-Carbo) Comparative, prospective, open-labeled, randomized phase II study of Cisplatin or Carboplatin with Gemcitabine in combination with Irinotecan-loaded beads (LC or ONCOZENE) versus Cisplatin or Carboplatin with Gemcitabine alone in the treatment of patients with unresectable intra-hepatic cholangiocarcinoma.
1.2 Objectives	The primary objective of this study is to confirm the efficacy of Irinotecan-loaded beads (LC or ONCOZENE), in combination with Gem-Cis or Gem-Carbo intravenous chemotherapy versus Gem-Cis or Gem-Carbo intravenous chemotherapy alone in the treatment of unresectable intra-hepatic cholangiocarcinoma. Open label, prospective, randomized phase II study.
1.3 Study Sponsor	Robert C.G. Martin, M.D., PhD University of Louisville
1.4 Primary Investigator	Charles R. Scoggins M.D., MBA
1.5 Co-investigators	Lawrence Kelly, M.D., Kelly M. McMasters, M.D., Ph.D., Prejesh Philips, M.D., Rebecca Redman, M.D., Vivek Sharma, M.D., Cliff Tatum, M.D.
1.6 Study Device	Biocompatibles' LC beads loaded with Irinotecan (70-150 µm or 100–300µm) or Celonova's ONCOZENE beads (40 µm or 75 µm) loaded with Irinotecan. Maximum total dose will be 100mg Irinotecan per procedure in combination with Gem-Cis or Gem-Carbo alternating on a 3 week schedule
1.7 Primary Endpoint	Primary endpoint will be tumor response according to modified RECIST Criteria
1.8 Secondary Endpoint	▪ Local Tumor Response (extent of necrosis in the treated lesions) ▪ Progression Free Survival ▪ Hepatic Progression Free Survival ▪ Change in Tumor Markers ▪ Overall Survival (telephone follow-up) ▪ Patient Tolerance
1.9 Study Design	Prospective, open-label, randomized phase II study to compare subjects treated with LC beads loaded with Irinotecan or ONCOZENE beads loaded with Irinotecan in combination with Gem-Cis or Gem-Carbo chemotherapy to subjects treated exclusively with Gem-Cis or Gem-Carbo. chemotherapy.
1.10 Number of Subjects	54 subjects will be enrolled and randomized 1 to 1 (27 in each arm).

1.11 Eligibility Criteria	***Inclusion:*** • Subjects over 18 years of age, of any race or sex, who have histological evidence of intrahepatic cholangiocarcinoma, who have been deemed unresectable by an experienced hepatic surgeon, and who are able to give informed consent, will be eligible • Subjects with at least one measurable liver tumor, with size > 1cm (modified RECIST criteria) • Subjects with liver-dominant disease defined as ≥80% of the subject's total amount of malignant disease (tumor burden) that is confined to the liver • Hematologic function: ANC ≥ 1.5 x 10^9/L, platelets ≥ 75 x10^9/L, INR ≤1.3 (subjects on therapeutic anticoagulants are not eligible if they cannot stop their anti-coagulation prior to DELTIC TACE and meet INR criteria) • Adequate liver function as measured by: Total bilirubin ≤ 2.0 mg/dl, AST and ALT ≤ 5 ULN, albumin ≥ 2.5 g/dl • Adequate renal function as measured by: Creatinine ≤ 2.0 mg/dl, > 50 ml/min calculated by the C-G equation • Non-pregnant women of child bearing potential and fertile men are required to use effective contraception (negative βHCG for women of child-bearing age) • Signed, written informed consent • ECOG status ≤ 2 • Liver tumor volume is less than 70% of entire volume of liver. (Less than 70% tumor replacement) ***Exclusion:*** • Subject eligible for curative treatment (i.e. resection or tumor ablation) • Active bacterial, viral or fungal infection within 72 hours of study entry • Women who are pregnant or breast feeding • ECOG Performance Status score of ≥3 • Life expectancy of < 3 months • PTT > 2.5 ULN and Hgb < 8.0 mg/dl • Patients with a history of Gilberts Syndrome • Patients with a history of UGT1A1 deficiency • Allergy to contrast media that cannot be managed with standard care (e.g. steroids), making magnetic resonance imaging (MRI) or computed tomography (CT) contraindicated • Presence of another malignancy with the exception of cervical carcinoma in situ and stage I basal or squamous cell carcinoma of the skin within 5 years of study entry.

	• Any contraindication for hepatic embolization procedures: - Large shunt as determined by the investigator (pretesting with TcMMA not required) - Severe atheromatosis vascular disease that precludes arterial cannulization - Hepatofugal blood flow - Main portal vein occlusion (e.g. thrombus or tumor) • Other significant medical or surgical condition, or any medication or treatment, that would place the subject at undue risk and that would preclude the safe use of chemoembolization or would interfere with study participation • Subjects with prior contraindications for the use of Irinotecan, gemcitabine, Cisplatin or Carboplatin • Subjects who have received prior systemic therapy with either Irinotecan, Gemcitabine, Cisplatin or Carboplatin • Subjects taking medications that may counteract the study medications. These medications include CYP3A4 inducers, such as Rifabutin and St. John's Wort, and CYP3A4 inhibitors such as Ketoconazole.

1.12 Chemo-embolization Procedure	Using a unilateral femoral (or brachial, if femoral artery is not available) approach, selective catheterization of the hepatic artery will be performed. Vascular access is obtained via the common femoral artery and a guidewire advanced under fluoroscopic guidance. A microcatheter is then inserted over the guidewire. The superior mesenteric artery is selected and an angiogram performed to identify any aberrant arterial anatomy and verify antegrade portal vein flow (on all embolization visits after the first, occlusion of vessels embolized on the previous visit should be recorded in the CRF). The celiac axis is then selected and an angiogram completed. The catheter and guidewire are used to select the proper hepatic artery and a limited angiogram performed to identify the branches of the hepatic artery. The right or left hepatic artery is selected distal to the cystic artery (if visualized), depending on the location of the lesions to be treated. Once the vascular supply of the tumor is identified, lobar to selective chemoembolization of the supplying artery is performed. At the discretion of the interventional radiologist, extrahepatic vessels may be prophylactically embolized in order to mitigate risk of non-target deposition of LC beads loaded with Irinotecan or ONCOZENE beads loaded with Irinotecan. Subjects with unifocal tumors will be treated with super selective chemoembolization. At the discretion of the investigator, a microcatheter may be used to select a second or third-order branch of the right or left hepatic artery in close proximity to the tumor. For multifocal disease or tumor spanning both lobes, embolization of each lobe will be performed separately on different treatment days. Once the catheter is in place within the artery feeding the tumor, the LC beads or ONCOZENE beads loaded with Irinotecan will be delivered into the artery. The objective of the embolization procedure will be to deliver up to 2 mL (1 vial, 100 mg Irinotecan) of the 70-150 µm or 100-300 µm L C beads. If ONCOZENE beads (40 µm or 75 µm) loaded with Irinotecan are used, then up to 2ml (1 vial, 100mg Irinotecan) of the 40 µm or 75 µm beads will be used. Radiological non-ionic contrast (preferably Omnipaque) will be used to guide the injection of beads. The beads will be mixed with contrast (according to the instructions for use) immediately prior to the procedure and injected slowly in 1ml aliquots using a "sandwich technique" (i.e. beads then contrast) in order to identify and minimize reflux. Catheter selection will be by operator preference (e.g. the choice of a microcatheter, in case of tortuous, narrow or spastic vessels). If vasospasm occurs, vasodilators may be given at the investigator's discretion. If the vasospasm does not resolve, the procedure should be aborted and the subject rescheduled. The catheter will then be removed and hemostasis achieved by manual compression or closure device. Each subject will observed for vital signs, femoral access site, pain management and fluid hydration per each institution's standard of care. The amount of contrast agent delivered to the subject during the procedure and dose of irradiation will be recorded as well as the time exposed to fluoroscopic imaging. The vessels embolized will be noted and the amount of embolic agent used will be recorded. All medications used during the procedure will be recorded, including pain management regimen.

1.13 Study Procedures: Baseline	Consented subjects will have the following screening/baseline assessments performed prior to the first treatment. Within approximately four weeks of the first treatment: • Detailed medical history including previous cancer history and cancer treatment, any medications taken within 30 days prior to study treatment, and any additional cancer-related medications taken one year prior to study start will also be recorded • Physical examination including weight, height and vital signs • Laboratory tests (w/ baseline): CBC, CMP, tumor marker (CA19-9) and coagulation (PT, PTT, INR) • Demographics • Serum pregnancy test (for women of child bearing potential) • Documentation of disease status (via a triple phase, thin cut (< 2.5 mm) contrasted CT or dynamic MRI of the abdomen and pelvis) All sites of disease should be identified by MRI or CT of abdomen/pelvis as well as contrasted CT chest and recorded at baseline. At least one measurable hepatic lesion must be identified as a target lesion and measured. This scan must be performed within approximately 4 weeks prior to first treatment.
1.14 Study Procedures during Treatment Period: Chemoembolization Visits	**Test Group** Subjects in the "Test Group" will receive chemoembolization(s) with Irinotecan-loaded LC beads or ONCOZENE beads in combination with intravenous chemotherapy. This group will receive chemoembolization(s) throughout the treatment period. The following data will be collected from subjects in the "Test Group" before and after each chemoembolization procedure: • Vital signs • Laboratory Tests: CBC, CMP and magnesium (coagulation as clinically indicated) • Adverse Event Monitoring and Concomitant Medication monitoring **Control Group** Subjects in the "Control Group" will receive intravenous chemotherapy **only** and will not receive any chemoembolization procedures for the duration of the study.
1.15 Study Procedures during Treatment Period: Chemotherapy Visits	**Test Group and Control Group** Subjects in both the "Test Group" and in the "Control Group" will have the following data collected prior to each systemic chemotherapy infusion: • Physical Exam or Nursing Assessment • Vital signs • Laboratory Tests: CBC, CMP and magnesium (coagulation as clinically indicated) • Adverse Event Monitoring and Concomitant Medication monitoring After every 3 chemotherapy cycles, subjects will have their first follow-up CT scan and office visit to assess tumor response to treatment.

1.16 Study Procedures: Follow-up Visits	**Test Group and Control Group** Subjects in both the "Test Group" and in the "Control Group" will remain on study until either progression of disease or until discontinuation of study treatments. Subjects will then enter into the Follow-Up period, which lasts for approximately 1 year following their last study treatment. During the Follow-Up period, subjects should be assessed and radiologically evaluated every 3 – 4 months, as per standard procedures. The following data will be collected during these standard, routine follow-up office visits: • Physical Examination • Vital signs • Laboratory Tests: CBC, CMP and tumor markers (CA19-9) • Tumor Marker Assessment (approximately every three months) CT/MRI of abdomen/pelvis (via a triple phase, thin cut (< 2.5 mm) contrasted CT or dynamic MRI of the abdomen and pelvis) for tumor response. • Adverse events and concomitant medications will be collected on each subject for up to 30 days after their last active study treatment.
1.17 Evaluation Procedures	• The primary endpoint will be tumor response rate measured from first treatment until progressive disease is reported (as defined by the modified RECIST criteria) • Tumor response will be defined as the best overall response according to modified RECIST criteria over all follow up visits from commencement of the first treatment • Local tumor response will be defined as best response using extent of necrosis in the treated lesions over all follow up visits • Hepatic progression free survival will be measured from first treatment until progression occurring in the liver, as defined by RECIST criteria • Change in tumor markers (CA 19-9) will be measured throughout the study • Overall survival will be determined by telephone follow-up after 12 months
1.18 Statistical Considerations	54 subjects will be enrolled into the study and randomized to combination therapy or systemic therapy in a 1:1 fashion. Subjects exhibiting complete or partial response will be classified as responders and all other subjects as non-responders. The response rate in the intravenous chemotherapy group can be assumed to be 25% and we expect to see response rates of 70% in the chemoembolization with LC or ONCOZENE beads loaded with Irinotecan group. The sample sizes in the table provide 80% power for a Fisher's exact test to detect the given difference between the assumed proportions at a significance level of 0.05.
1.19 Endpoints	▪ Proportion of subjects completing scheduled treatment plan ▪ Safety: Serious adverse events and Dose limiting toxicities ▪ Efficacy: Response to Treatment and Survival

2 Investigational Plan

2.1 Study Objectives

The primary objective of this study is to evaluate the safety and efficacy of LC beads, loaded with Irinotecan, or the ONCOZENE beads, loaded with Irinotecan, in combination with intravenous chemotherapy versus intravenous chemotherapy alone in the treatment of unresectable intrahepatic cholangiocarcinoma.

2.2 Study Design

This is an open label, prospective, randomized, controlled phase II study designed to assess the clinical performance of chemoembolization with LC or ONCOZENE beads, loaded with Irinotecan, in combination with Gem-Cis or Gem-Carbo intravenous chemotherapy versus Gem-Cis or Gem-Carbo intravenous chemotherapy alone in the treatment of unresectable intrahepatic cholangiocarcinoma.

2.3 Primary Endpoint

The primary endpoint will be tumor response according to modified RECIST Criteria.

2.3.1 Tumor Response

Prior to 1994, the assessment of antitumor effect of a treatment was generally determined in accordance with the World Health Organization (WHO) criteria established in the late 1970s. The WHO criteria assess the change in tumor size using two perpendicular measurements of lesions.

The WHO criteria were reviewed in the 1990s leading to the development of a new set of criteria called Response Evaluation Criteria in Solid Tumors (RECIST).[41] RECIST considers the change in tumor size using the sum of uni-dimensional measurements of the longest diameter in up to five target lesions per organ (or ten in total, representing all involved organs) and also accounts for non-measurable lesions. Since then it has been modified with the recent publication taking into account changes in vascularity. Similarly, metastatic colorectal cancer response is more commonly assessed by PET scan and reduction in Standardized Uptake Values (SUV) counts. This protocol will use both the modified RECIST criteria and PET scan intensity to evaluate liver specific response and extra-hepatic disease response.

2.3.1.1 Modified RECIST Criteria

Modified RECIST is currently accepted as the basis for assessing antitumor activity in all solid tumor types and is endorsed by regulatory authorities.[42]

2.3.1.1.1 Measurement and identification of target lesions

Subjects must have at least one measurable lesion, defined as >20 mm using CT or MRI or >10 mm using spiral CT. When disease is restricted to a solitary lesion, its neoplastic nature must be confirmed by cytology/histology.

Baseline measurements must be taken within four weeks prior to commencement of treatment. The same measurement technique (CT/MRI) must be used at baseline and follow up. No more than 5 target lesions in the liver and 10 lesions in total, representative of all sites involved, will be identified. Those with the largest diameters should be included.

All other (non-target) lesions should be reported but not measured, in order that their presence or lack thereof may be tracked at follow up.

2.3.1.1.2 Criteria for target lesions

Complete Response:	Disappearance of all target lesions or disappearance of all arterial enhancements in the target lesion
Partial Response:	At least 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum of longest diameter, or ≥30% loss of arterial enhancement
Progressive Disease:	At least 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameters recorded since start of treatment, OR appearance of one or more new lesions
Stable Disease:	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum of the longest diameters recorded since start of treatment

2.3.1.1.3 Criteria for non-target lesions

Complete Response:	The disappearance of all non-target lesions AND normalization of tumor marker level
Incomplete Response/Stable Disease:	Persistence of one or more non-target lesions AND/OR maintenance of tumor marker level above normal limits
Progressive Disease:	Appearance of one or more new lesions AND/OR unequivocal progression of existing non-target lesions (progression of non-target lesions will be determined at the investigator's discretion)

2.3.1.1.4 Response evaluation and reporting

Tumor response will be evaluated at approximately 10 weeks by abdominal CT/MRI following the first round of treatments (3 total cycles of chemotherapy). Tumor response will again be evaluated by abdominal CT/MRI following any additional rounds of treatment (3 cycles increments of chemotherapy) and/or at approximately 10 week (if dose limiting toxicities are experienced). After study treatment is discontinued, tumor response will be evaluated every 3-4 months for a total of 12 months post-last active study treatment. After each radiographic evaluation, response in target and non-target lesions along with presence of any new lesions will be reported on the CRF. Overall

response will be assigned by combining the response in target lesions, non-target lesions, and the appearance or lack of new lesions as outlined in the table below.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

2.3.1.1.5 Evaluation of best overall response

The best overall tumor response (according to modified RECIST) is defined as the best response from start of treatment over all follow up visits or until disease progression/recurrence whichever comes first.

2.4 Secondary Endpoints

The secondary endpoints will include:

- Local tumor response (extent of necrosis in the treated lesions)
- Time to progression
- Hepatic Progression Free Survival
- Change in tumor markers
- Overall survival
- Patient Tolerance

2.4.1 Subject Tolerance

Safety assessments will include physical examinations, vital signs, clinical laboratory profile and adverse events.

All observed toxicities and side effects will be graded according to NCI Common Toxicity criteria v.4.0 toxicity criteria for all subjects and the degree of association of each with the procedure assessed and summarized.

Treatment related Serious Adverse Events rate (SAE) — defined as SAEs considered possibly, probably or definitely related to treatment — will be determined.

2.4.1.1 Response evaluation and reporting

Tumor response will be evaluated by CT/MRI after every third cycle of systemic chemotherapy at approximately 10, 20, and 30 weeks following the first treatment. The primary efficacy time point will be after the 10-week visit. At each follow-up visit that requires CT/MRI evaluation, the diameter, percentage necrosis and viable diameter for each target lesion will be reported in the CRF.

2.4.1.1.1 Evaluation of best overall response

The best overall response is defined as the best response from start of treatment over all follow-up visits or until disease progression/recurrence.

The protocol acknowledges that this assessment of local tumor response is not a validated method, but will provide useful information on the assessment of necrosis following locoregional treatment with LC or ONCOZENE beads loaded with Irinotecan.

2.4.2 Time to Progression

Overall time to progression to include all hepatic disease and extra-hepatic disease will be recorded to assess both organ specific and systemic response rates between both treatment arms.

2.4.3 Time to Liver Progression

Liver specific time to progression will also be recorded to better assess the response rates and duration of response to combined liver directed therapy when compared with systemic therapy alone.

2.4.4 Change in Tumor Markers

CA 19-9 and will be measured at baseline and every 3 months. Values will be assessed for clinical significance.

2.4.5 Overall Survival

Overall survival will be determined using Long-Term Follow-up visits and/or by telephone or standard physician follow-ups as per standard of care until death.

2.5 Study Population

2.5.1 Number of Subjects

Up to 54 subjects will be enrolled. These subjects will be randomized into group 1: Gem-Cis or Gem-Carbo systemic chemotherapy only group (Control Group) or group 2: Gem-Cis or Gem-Carbo systemic chemotherapy plus chemoembolization with LC or ONCOZENE beads (Test Group) (1:1 in each arm).

2.5.2 Selection Criteria

Subjects will be eligible for the study if they fulfill the following entry criteria.

2.5.2.1 Inclusion Criteria

- Subjects over 18 years of age, of any race or sex, who have histological evidence of intrahepatic cholangiocarcinoma, who have been deemed unresectable by an experienced hepatic surgeon, able to give informed consent
- Subjects with at least one measurable liver metastases, with size > 1cm (modified RECIST criteria)
- Subjects with liver-dominant disease, defined as ≥80% of the subject's total amount of malignant disease (tumor burden) that is confined to the liver

- Fertile men and non-pregnant women of childbearing potential who have agreed to use an acceptable method of birth control. Women of child bearing potential must have a negative βHCG (serum or urinalysis) to be eligible.
- Hematologic function: ANC ≥ 1.5 x 10^9/L, platelets ≥ 75 x10^9/L, INR ≤1.3 (subjects on therapeutic anticoagulants are not eligible if they cannot stop their anti-coagulation prior to DELTIC and meet INR criteria)
- Adequate liver function as measured by: Total bilirubin ≤ 2.0 mg/dL, AST and ALT ≤ 5 ULN, albumin ≥ 2.5 g/dL
- Adequate renal function as measured by: Creatinine ≤ 2.0 mg/dl, > 50 ml/min calculated by the C-G equation
- Signed, written informed consent
- ECOG status ≤ 2
- Liver tumor volume less than 70% of total volume of the subject's liver (i.e. less than 70% tumor replacement)

2.5.2.2 Exclusion Criteria

- Subjects eligible for curative treatment (i.e. resection or radiofrequency ablation)
- Active, untreated bacterial, viral or fungal infection within 72 hours of study entry
- Women who are pregnant or breast feeding
- ECOG Performance Status score of ≥3
- Life expectancy of < 3 months
- PTT > 2.5 ULN and Hgb < 8.0 mg/dL
- Patients with a history of Gilbert's Syndrome
- Patients with a history of UGT1A1 deficiency
- Allergy to contrast media that cannot be managed with standard care (e.g. steroids), making magnetic resonance imaging (MRI) or computed tomography (CT) contraindicated
- Presence of another malignancy with the exception of cervical carcinoma in situ and stage I basal or squamous carcinoma of the skin
- Any contraindication for hepatic embolization procedures:
  - Large shunt as determined by the investigator (pretesting with TcMMA not required)
  - Severe atheromatosis vascular disease that precludes arterial cannulization
  - Hepatofugal blood flow
  - Main portal vein occlusion (e.g. thrombus or tumor)
- Other significant medical or surgical condition, or any medication or treatment, that would place the subject at undue risk and that would preclude the safe use of chemoembolization or would interfere with study participation
- Subjects with prior contraindications for the use of Irinotecan, gemcitabine, Cisplatin or Carboplatin

- Subjects who have received prior systemic therapy with either Irinotecan, gemcitabine, Cisplatin or Carboplatin
- Subjects taking medications that may counteract the study medications. These medications include CYP3A4 inducers such as Rifabutin, and St. John's Wort, and CYP3A4 inhibitors such as Ketoconazole.

2.6 Study Procedures and Methodology

2.6.1 Study Schedule and Guidelines for Visits

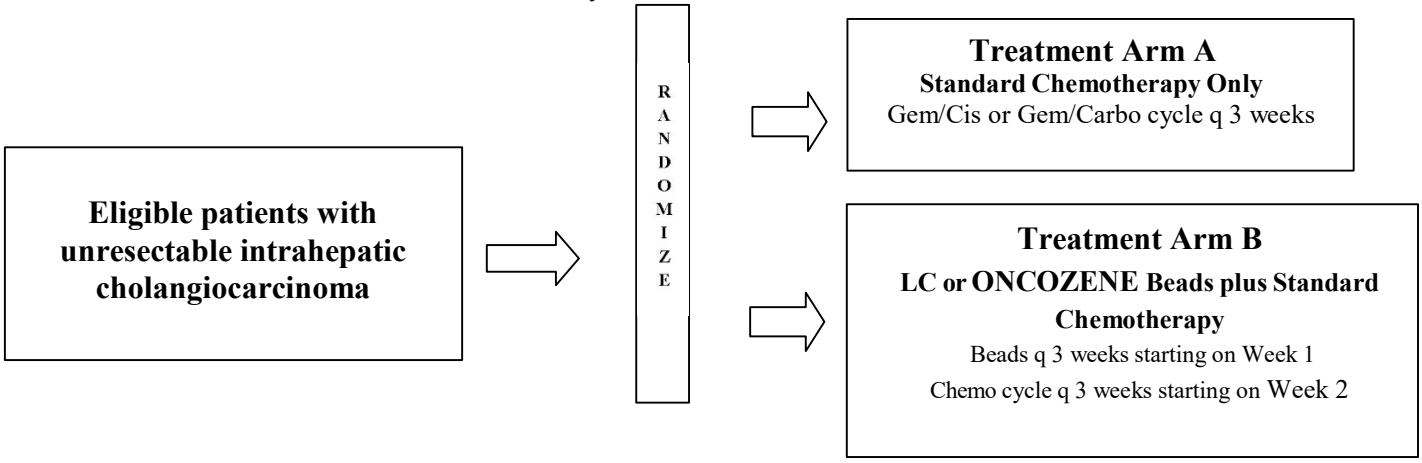
Subjects admitted for first line chemotherapy for unresectable intrahepatic cholangiocarcinoma will be reviewed for study eligibility. After checking suitability to enter the study, subjects who agree to participate must sign the informed consent form before undergoing any study related procedures or treatment.

2.6.1.1 Baseline Assessment

Occurs within four weeks of the first treatment:

- Detailed medical history including previous cancer history and cancer treatment. Any concomitant medications taken up to 30 days prior to the first study treatment will be recorded.
- Physical examination including weight, height and vital signs (height will be collected at baseline only)
- Laboratory tests CBC and CMP; tumor markers: CA 19-9; and coagulation (baseline and as clinically indicated): P
- Demographics
- Pain score-graded using a standard ten point pain scale
- Performance Status (ECOG)
- Serum pregnancy test (for women of child bearing potential)
- Documentation of disease status:
- All sites of disease should be identified by dynamic MRI or contrasted CT of abdomen/pelvis as well as contrasted CT chest and recorded at baseline. At least one measurable hepatic lesion must be identified as target lesion and measured. This scan will be performed within 4 weeks prior to first treatment.

The investigator will confirm the subject's eligibility after all baseline scans and laboratory results have been reviewed.



2.6.1.2 Treatment Period

2.6.1.2.1 TEST GROUP

Subjects randomized to the Test Group will receive chemoembolization with the Irinotecan loaded LC beads or the Irinotecan loaded ONCOZENE beads plus systemic chemotherapy consisting of Gemcitabine/Cisplatin or Gemcitabine/Carboplatin in the following fashion:

- Chemoembolization with Irinotecan loaded beads (LC or ONCOZENE) performed every 3 weeks, starting on Week 1.*
- Cisplatin at 25 mg/m2 given as a 2-hour IV infusion on Days 1 and 8, starting on Week 2.

  OR
- Carboplatin dose (mg) = (target AUC) x (GFR + 25) with target AUC = 4 given as a 2-hour IV infusion on Day 1 only starting on Week 2. The maximum dose for AUC of 4 is 600 mg.

  AND
- Gemcitabine at 1000 mg/m2 given as a 30-minute IV infusion following Cisplatin on Days 1 and 8, starting on Week 2.

If the treating medical oncologist feels that Cisplatin is not recommended for the subject based on performance status or tolerance then Cisplatin can be replaced with Carboplatin on a case by case decision with the Sponsor. The Carboplatin dose will be based on a Target Area Under the Curve of 4 using the Calvert Formula of Total Carboplatin Dose (mg) = Target AUC x (GFR+25). The maximum dose for AUC of 4 is 600 mg.

The first chemotherapy treatment will occur one week after the first chemoembolization procedure and will occur during Week 2 of the study calendar. Each chemotherapy cycle is repeated every 3 weeks (21 days).

All doses will be based on the subject's actual weight. The actual weight at screening will be used to calculate body surface area (BSA). Some institutions may have a BSA maximum of 2.0 which may be used; however, the BSA should be recalculated if a subject's weight changes by ≥10%.

All treatment regimens will be given until progression of disease or until the treating physician determines it is in the subject's best interest to discontinue therapy.

* It is anticipated that each subject randomized to the Test Group will receive two chemoembolizations (minimum 3 weeks apart) during their treatment period. Subjects in the Test Group may receive additional chemoembolizations, if needed. Guidance for repeat treatments is at the treating physician's discretion and based on the subject's response and tolerance to treatment along with the subject's overall burden of disease. With chemoembolization procedures, it is routine care to assess a subject's tumor response using CT or MRI imaging every 10-12 weeks. These intervals are long enough to reflect

the amount of tumor necrosis and short enough to reveal tumor recurrence or progression.

2.6.1.2.1.1 Irinotecan DEB

The Test Group will receive chemoembolization using Irinotecan-loaded LC Beads, using up to 2 mL of Irinotecan-loaded LC beads (bead size: 70-150 μm or 100-300 micron; 100mg Irinotecan) or Irinotecan-loaded ONCOZENE beads, using up to 2 mL of Irinotecan-loaded ONCOZENE beads (bead size: 40 μm or 75 μm; 100 mg Irinotecan).

The following assessments will be made within 24 hours prior to LC or ONCOZENE bead chemoembolization procedure:

- Vital signs
- Physical Exam / Nursing Assessment
- Laboratory Tests (CBC, CMP, magnesium) (may be performed up to 72 hours prior)
- Adverse Event Monitoring
- Concomitant Medication monitoring

2.7 Chemoembolization Procedure

The following procedures will be followed for each chemoembolization treatment.

2.7.1 Pre Treatment

The subject should be nil by mouth overnight prior to the treatment. Subjects will be adequately pre-medicated according to standard hospital procedure. Subjects will have a venous line inserted prior to therapy and hydration will be scheduled according to clinical needs. Analgesics, anti-emetics and prophylactic antibiotic therapy will be given at the discretion of the investigator except for aprepitant and dexamethasone which should be dosed according to this protocol.

Due to potential drug-drug interactions, the use of aprepitant (Emend) and dexamethasone (Decadron) for antiemetic therapy should be assessed and appropriate substitutes considered for ALL subjects randomized to the Treatment Group and receiving chemoembolizations.

However, if alternative medications are not felt to be adequate for controlling the side effects of chemotherapy, the CAUTIOUS use of these drugs may be clinically warranted. This determination will be based on the treating physician's discretion and should be reflected in the AEs and SAEs for the subject. If these drugs are utilized, the AEs and SAEs for the subject will need to be followed with additional focus looking for any effects of potential drug interactions.

Aprepitant (Emend) and dexamethasone (Decadron) should be dosed in the following fashion:

- Aprepitant 125 -150 mg intravenously with chemotherapy infusion
- Dexamethasone 10-12 mg intravenously with chemotherapy infusion

2.7.2 Pain Management

In prior studies of chemoembolization with LC beads loaded with Irinotecan, all subjects reported moderate post procedural pain. It is recommended that a strong opioid (e.g. Morphine) parenteral be used for the procedure. Intra-arterial lidocaine (2-4cc) prior to injection of loaded beads may be used at the investigator's discretion.

2.7.3 Loading Procedure for LC or ONCOZENE Beads Loaded with Irinotecan

The instructions are for a dose of up to 100 mg of Irinotecan to be delivered in 1 vial of LC or ONCOZENE beads at a dose of 50 mg/mL of LC beads or ONCOZENE beads. Irinotecan is available as Campto solution at 100mg/vial (5 mL at a concentration of 20 mg/mL), and it is these vials that are recommended for use.

Irinotecan Dose Required	Volume of Bead Required	Volume of Bead vials, containing 2 mL of Beads
100 mg	2 mL	1 vials

The instructions are to load 100 mg Irinotecan into 1 vial containing 2 mL of LC or ONCOZENE beads at a dose of 50 mg per mL of LC or ONCOZENE beads.

2.7.3.1 Preparation of LC or ONCOZENE Bead

Remove as much saline as possible from each vial of beads using a syringe with a small gauge needle or filter needle. This step usually takes 5- 10 minutes depending on experience.

2.7.3.2 Loading of LC or ONCOZENE Bead

Using a syringe and needle add a total of 5 mL of Campto solution (20 mg/mL) directly into each vial of beads.

Agitate the beads/Campto solution gently to encourage mixing then allow the solution to stand until beads are loaded. The LC beads will appear turquoise and the ONCOZENE beads will appear red when the loading is completed. For this static loading the following times should be used to give at least 90% loading of the dose into LC or ONCOZENE beads:

Product Cap Color	Nominal Size Range (µm)	Time to give >90% Loading	Actual Amount Loaded
Yellow	100-300	2 h	98%
Black and Yellow	70 - 150	2 h	98%
Black	40	30 minutes	98%
Maroon	75	30 minutes	98%

After loading, LC and ONCOZENE beads should be stored at room temperature or refrigerated. Transfer the vials of loaded beads to Radiology when requested.

2.7.3.3 Preparation for Use

Prior to use, transfer the LC or ONCOZENE beads loaded with Irinotecan to a 20 mL syringe and add an equal volume of non-ionic contrast media [~7 mL (5 mL of Campto + 2 mL of beads)]. This step will take 2-15 minutes again depending on experience. Invert the syringe gently and wait 1 to 15 minutes to obtain an even suspension of LC or ONCOZENE beads.

Contrast media should be added immediately prior to use.

2.7.3.4 Similarity of Both Beads:

ONCOZENE microspheres are FDA cleared (Registration# K130307) as a Class II device (Product Code: KRD) for the "embolization of hypervascular tumors and arterial-venous malformations". This is the same FDA indications as Quardaspheres (Merit Medical) and LC Beads (Biocompatibles). As with the competition microspheres drug loading and delivery are "Off label" indications.

ONCOZENE/ONCOZENE microspheres are hydrogel core, flexible and compressible polymer microsphere with a polymethacrylate backbone surface coated with a thin (nm) shell of PolyzeneÒ-F coating (high molecular weight, ultrapure, biocompatible polymer of polyphosphazene). They are unique in that they come in three sizes (40 ± 10 μm; 75 ± 15 μm; and 100 ± 25 μm) and are the smallest available microspheres for DEB-TACE (Drug-Eluting Bead-Transarterial Chemoembolization). Small drug eluting microspheres have been reported to cause a higher degree of tumor necrosis. ONCOZENE/ONCOZENE microspheres can load drugs faster than the competition (doxorubicin powder made to 20 mg/ml solution loads in 1 hour, and irinotecan solution loads in 30 minutes). The microspheres can load more doxorubicin per ml microspheres (50 mg/ml versus 37.5 mg/ml for LC Beads or LC M1)(2 ml syringe of ONCOZENE Microspheres can load 100 mg doxorubicin, does not need 2 unit of competition device to deliver 100 mg) . This is 33% more deliverable drug unit. They are stable after drug loading which equates to no microsphere shrinkage.

In vitro drug release time for ONCOZENE/ONCOZENE microspheres is slower than reported competition in vitro release rates. Therefore, slower drug elution causes lower systemic drug levels and slower drug elution can cause prolonged and higher drug tissue concentrations. For Irinotecan used in treating mCRC, in animal studies using a VX2 tumor model, ONCOZENE-irinotecan showed reduced systemic exposure to Irinotecan, higher and prolonged tumor drug concentration, and higher necrosis versus IA and IV administration.

ONCOZENE/ONCOZENE microspheres come in convenient 2 ml or 3 ml syringes that can load and deliver 100 mg to 150 mg of the desired drug via trans-arterial embolization of the tumor(s) lesions.

ONCOZENE microspheres have been used in Europe to treat HCC. ONCOZENE microspheres (3 ml syringe loaded with 150 mg doxorubicin) have been administered to patients with the following results:

- 17 patients underwent 33 DEB-TACE procedures with no treatment related deaths

- Embolizations were to stasis in all 2^{o} segmental arteries.

- Post-embolization syndrome (PES) was reported in 8 out of 33 procedures (25%) which is lower than traditional Deb-TACE. Other adverse events (10 out of 33) were Grade II or lower.

- Initial tumor control at 4 weeks was 100% (17/17) and at 12 weeks (6/7 = 86%). This study is ongoing.

A case report using ONCOZENE-Irinotecan is below. Andreas Saleh, MD., Institute for Diagnostic and Interventional Radiology and Infant Radiology, Clinical Center of Schwabing, Germany treated 2 patients with ONCOZENE-IRI.

- Patient #1: A 60 year old patient with reoccurring mCRC at resection edge was treated with ONCOZENE-IRI (40 µm loaded with 37.5 mg irinotecan). At follow-up (5 months) tumor is in regression with no revascularization.

- Patient #2: A 72 year old patient with reoccurring pulmonary and liver metastases, with resection of pulmonary metastases (3 months before DEB-TACE), was treated with ONCOZENE- IRI (1.3 ml of ONCOZENE-IRI, loaded with 67 mg irinotecan in 1.3 ml). Immediate post embolization fluorography showed total devascularization of the lesion. 6 month CT showed no reoccurrence of tumor.

ONCOZENE-IRI has been used in the U.S. at several institutions. There are no published reports to date. Anecdotal information included the following:

- 100 µm ONCOZENE microspheres loaded with 100 mg of Irinotecan have been used with no reported severe adverse events other than PES pain which has ranged from none to requiring overnight opioids. Treatment were lobar and sub-selective.

- Reports are that a single treatment has reduced tumor vascularization and stable disease to complete reduction of tumor lesion.

- The overall systemic exposure of Irinotecan from the ONCOZENE™ bead is similar to reduced when compared to the DEBIRI bead.

ONCOZENE-IRI versus DEBIRI in Animal Models and Humans

Model	Device	IRI Dose	Plasma T_{MAX}	Plasma C_{MAX} [ng/ml]	Plasma $T_{1/2}$	AUC ng•hr/ml	Ratio $\frac{AUC_{D\,EB}}{AUC_{IV}}$ (% ↑or↓)	[Tissue] ng•hr/ml	Reference
Sheep	DEBIRI (DC 300-500µm)	50 mg	5 min	663	~1.0 hr	56862	0.410 59% ↓	See below	Baylatry et al. 2011. J Biomed

									Mat Res B: App Biomat. 99B:351
Rabbit VX2	DEBIRI (Pre-loaded DC 100-300 µm with 100 mg IRI/ml rehydrated microspheres)	6-16.5 mg (Dosed to stasis, so each tumor received a different amount of drug)	10 min	189.7	4.1 hr	$7939_{0\text{-}2\ hr}$ $18468_{2\text{-}24\ hr}$ (ng•min/ml)	ND	See below	Rao et al. 2012. Cardiovas Intervent Radiol. 35:1448
	ONCOZENE-IRI (40 µm ONCOZENE) (50 or 25 mg IRI/ml microspheres)	4.2 mg	60 min	172	3.16 hr	2158*	0.034 96%↓	See below	Internal data
		8.33 mg	30 min	351	3.15 hr	4656*	0.073 93% ↓		
Pig	*D*EBIRI (DC100-300 µm)	200 mg (25, 50, 100, or 200 mg IRI)	2 min	1791	~3.5 hr	ND	0.99++	ND	Taylor et al. 2007. Eur J Pharmaceutical Sci. 30:7-14
	DEBIRI DC100-300 µm pre-loaded with100 mg IRI/ml lyophilizedbeads)	100 mg	10 min	1532	3.35 hr	7307**	1.11≡ 11%↑	ND	Lewis et al. 2013. J Mat Sci: Mater Med. 24:115-127
	ONCOZENE-IRI 75 µm	50 mg	20 min	95.6	2.45 hr	39295*	0.106 89%↓	See below	Just completed Internal data
	DEBIRI (DCM1 $_{70\text{-}150\ µm}$)	50 mg	10 min	170.9	1.3 hr	49722*	0.134 87%↓	See below	
Human	DEBIRI	100-400 mg	2 hr	194	4.6 hr	1680	ND	ND	Eichler et al. 2012. Internat J

									Oncology. 41:1213-1220
	DEBIRI	100 mg	1 hr	281	~4 hr	ND	ND	ND	Martin et al. 2012. J Gastrointest Surg. 16:1531

ND = not determined
T_{Max} = Time to Maximum Drug Concentration
C_{MAX}= Maximum Irinotecan Plasma Concentration
$T_{1/2}$ = Time to Reduce Irinotecan Concentration in Half
AUC = Area Under the Curve
* AUC Calculated assuming a bolus injection of irinotecan
** Not sure AUC is calculated the same way as Radeleff and Tanaka
≡ AUC calculation was not over total time frame, and is not truly comparable to Tanaka.
++ estimated from Figure 4A.

ONCOZENE-IRI and DEBIRI Drug Concentrations in Analyzed Tissues

Model	Device/Dose	[Tissue/Tumor irinotecan Concentration] ng•hr/ml
Sheep	DEBIRI	4 days = no detectable irinotecan or SN 38 28 days = no detectable irinotecan or SN-38
Rabbit VX2 (Rao et al)	DEBIRI (DC 100-300 µm pre-loaded with 100 mg IRI/ml) 6-16.5 mg (Dosed to stasis, so each tumor received a different amount of drug)	1 hr= 20.225 ng/g tissue irinotecan 6 hr = 42.08 ng/g tissue irinotecan 24 hr = 174.44 ng/g tissue irinotecan 1 hr= 1.95 ng/g tissue SN-38 6 hr = 4.65 ng/g tissue SN-38 24 hr = 70.25 ng/g tissue SN-38
Rabbit VX2 (Internal Data)	ONCOZENE-IRI 40 µm ONCOZENE Group 1 = 3.42 mg IRI Group 2 = 1.71 mg IRI Group 3 = 1.71 mg IRI	Group 1 24 hrs = 2842 ng/g tissue irinotecan Group 2 24 hrs = 857 ng/g tissue irinotecan Group 3 24 hrs = 1049 ng/g tissue irinotecan Group 1 72 hrs = 66 ng/g tissue SN-38 Group 2 72 hrs = 25 ng/g tissue SN-38 Group 3 72 hrs = 12 ng/g tissue SN-38
Pig (Internal Data DCM1 was used as a control)	ONCOZENE-IRI (75 µm ONCOZENE) 50 mg	24 hr = 680 ng/g tissue irinotecan 48 hr = 143 ng/g tissue irinotecan 72 hr = 130 ng/g tissue irinotecan 168 hr = 91 ng/g tissue irinotecan 24 hrs = 86.4 ng/g tissue SN-38 48 hrs = 37.5 ng/g tissue SN-38
Pig (Internal Data)	DEBIRI (DCM1 $_{70\text{-}150\ \mu m}$) 50 mg	24 hr = 832 ng/g tissue irinotecan 48 hr = 142 ng/g tissue irinotecan 72 hr = 141 ng/g tissue irinotecan 168 hr = 142 ng/g tissue irinotecan 24 hrs = 52.5 ng/g tissue SN-38 48 hrs = 0.0 ng/g tissue SN-38

Study # 1
Pig liver embolization with 75 μm ONCOZENE versus DCM1 (70-150 μm)

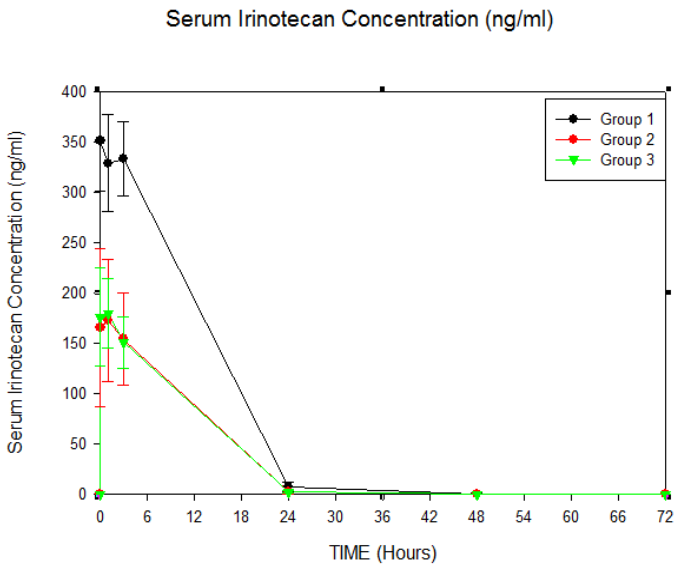
1. ONCOZENE is slower to release Irinotecan than DCM1.
2. Initial plasma levels of ONCOZENE-irinotecan are 2-3 times lower than DCM1.
3. Much higher SN-38 Tissue concentrations for ONCOZENE at both 24 and 48 hrs.
4. SN-38 is active form of Irinotecan and is converted intra-cellularly by carboxylesterase converting enzyme (CCE) in liver or colorectal tissue.

Working Hypothesis:
Irinotecan is activated via intra-cellular enzymes to SN-38 to be most effective in killing tumor/tissue. The reason that there is detectable levels of SN-38 at extended time periods (48 hrs.) after ONCOZENE embolization is that embolization with ONCOZENE microspheres which penetrate deeper in the tissue's micro-vasculature, due to smaller, uniform sizes, improves microsphere distribution (better coverage). The slower, controlled release of Irinotecan by ONCOZENE reduces systemic toxicities, and improves drug coverage, allowing for more localized enzyme activation of the irinotecan. (e.g. Better embolization of the micro-vascular structures with significantly more particles (10×10^6 ONCOZENE microspheres/ml versus 1.2×10^6 DCM1 microspheres) increases the probability that Irinotecan can be converted to SN-38 which in turn should lead to better tumor/tissue killing).

Study # 2
VX-2 Rabbit Study: A Dose Response Study of 40μm Irinotecan-loaded ONCOZENE™ Microspheres using a Rabbit VX2 Liver Cancer Model

Doses: 40 μm ONCOZENE 50 mg/ml microspheres or 40 μm ONCOZENE 25 mg/ml microspheres

Group 1 (3.42 mg irinotecan in 0.41 mls ONCOZENE)
Group 2 (1.67 mg irinotecan in 0.20 mls ONCOZENE)
Group 3 (1.563 mg irinotecan in 0.40 mls ONCOZENE)



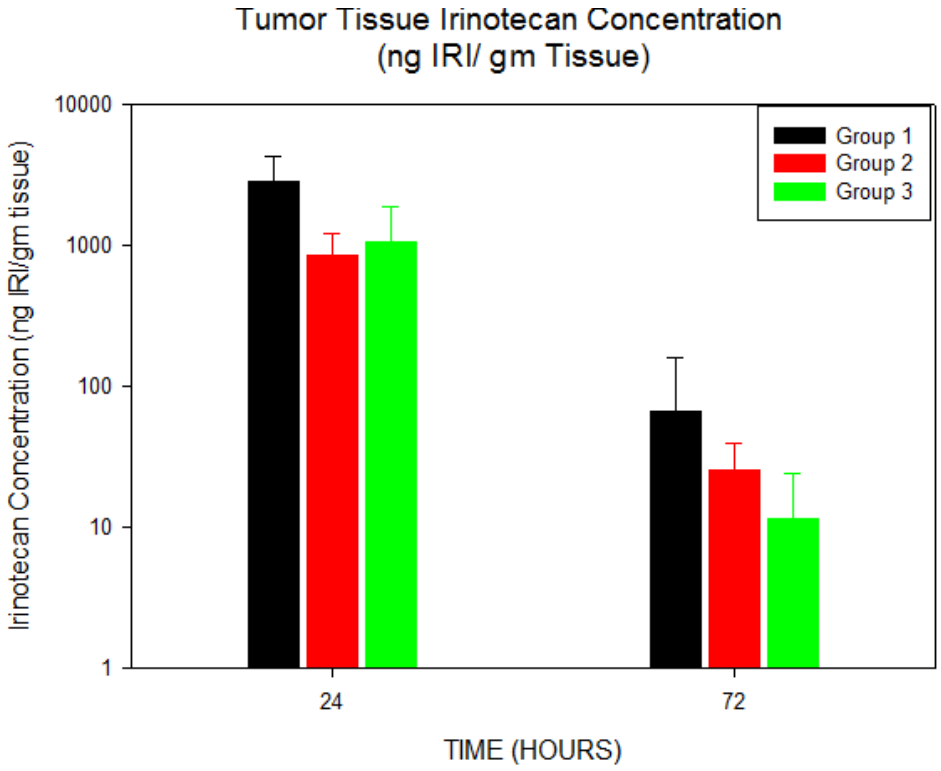
Group	AUC for Serum Irinotecan
Group 1 (3.42 mg Irinotecan)	4656.5 ng•hr/ml
Group 2 (1.67 mg Irinotecan)	2158.3 ng•hr/ml
Group 3 (1.63 mg irinotecan)	2145.6 ng•hr/ml

General Parameters

Pharmacokinetic Parameter	40 µm ONCOZENE-IRI		
	Group 1	Group 2	Group 3
C_{MAX}	351 ng/ml	172 ng/ml	180ng/ml
Time to C_{MAX}\	30 min	60 min	60 min
$T_{1/2}$ Beta Phase	$T_{1/2}$ =3.15 hrs.	$T_{1/2}$ = 3.16 hrs.	$T_{1/2}$ = 3.16 hrs.
AUC Irinotecan Plasma	4656.5 ng•hr./ml	2158.3 ng•hr./ml	2145.6 ng•hr./ml
AUC SN-38 Plasma	48.03 ng•hr./ml	20.54 ng•hr./ml	22.88 ng•hr./ml
Tissue Irinotecan at 24 hrs. ng/g Tumor	2842 ng/g tissue	857 ng/g tissue	1049 ng/g tissue
Tissue Irinotecan at 72 hrs. ng/g Tumor	66 ng/g tissue	25 ng/g tissue	12 ng/g tissue
% Tumor Kill at 24 hrs.	90% Necrosis	87% Necrosis	90% Necrosis
% Tumor Kill at 72 hrs.	70% Necrosis	63% Necrosis	65% Necrosis

% Tumor Kill at 168 hrs.	90% Necrosis	93% Necrosis	100% Necrosis

AUC for Systemic bolus of 3.42 mg Irinotecan with $T_{1/2}$ = 3 hrs = 63527 ng•hr/ml 4656/63527 = 7.3% of injected Irinotecan



Irinotecan IC_{50} is approxmately 10-20 nM (5.6-11.2 ng/ml). These results imply that at 72 hrs post-embolization there is still 11-62 ng Irinotecan per gram tissue which is 11-62 ng/gm tissue /1.06 gm tissue/ml = 10-58 ng/ml irinotecan. The tissue irinotecan concentrationis is still at a therapeutic level in the tissue (> IC_{50} level).

Conclusions:

1. Complete embolization using half dose IRI-loaded 40µm ONCOZENE (25mg IRI + 2ml ONCOZENE) achieved high tumor necrosis rate. This result indicates that precisely calibrated 40µm ONCOZENE microspheres could have an advantage to effectively occlude the tumor feeding vessels, which could induce tumor ischemic necrosis.
2. The liver dysfunction after TACE was significantly milder in the use of half dose IRI-loaded 40µm ONCOZENE, when compared with the use of full dose IRI-loaded 40µm ONCOZENE. In addition, the serum irinotecan concentration after TACE using half dose IRI-loaded ONCOZENE was significantly lower than that of full dose one. These results indicated that TACE using half dose IRI-loaded 40µm ONCOZENE could reduce the adverse effects in patients.
3. $T_{1/2}$ = 3.3 hrs About right for animal with heart rate of 130+ beats/min
4. Time to C_{MAX} is extended, which implies slower drug release.
5. Tissue irinotecan concentration remains above IC_{50} concentration for 72 hrs. Indicates slow release into tissue and prolonged tissue presence due to ischemic with small microspheres.

Thus the ability to utilize either the BTG LC beads or the Celonova ONCOZENE beads will be similar with the desired effect of delivered Irinotecan to the target multi-focal cholangiocarcinoma.

2.7.4 Chemoembolization with LC or ONCOZENE Beads loaded with Irinotecan

Subjects will receive chemoembolization using LC or ONCOZENE beads, loaded with Irinotecan. The size range for the LC beads to be used in the study will be 70-150 μm or 100-300 μm (nominal) with a dose of up to 100 mg Irinotecan per treatment. The size of ONCOZENE beads to be used in this study will be 40 μm or 75 μm with a dose up to 100 mg Irinotecan per treatment. No lipiodol will be used with LC and ONCOZENE beads, loaded with Irinotecan. The beads will be mixed with a non-ionic contrast media in the vial immediately prior to use according to the instructions for use.

2.7.4.1 Catheter Compatibility

The following catheter or an equivalent or larger French size catheter is compatible with the LC or ONCOZENE beads loaded with Irinotecan.

Trade Name	Manufacturer	Size
Progreat™ Micro Catheter System	Terumo Corporation, 44-1, 2- Chome, Hatagaya, Shibuya-Ku, Tokyo 151-0072, Japan	2.4Fr Minimum outer diameter (O.D.) of 2.4Fr. (0.80mm) on the usable length of the catheter.

2.7.4.2 Embolization Procedure

Vascular access is obtained via the common femoral artery and a guide wire advanced under fluoroscopic guidance. A diagnostic catheter is then inserted over the guide wire. The superior mesenteric artery is selected and an angiogram performed to identify any aberrant arterial anatomy and verify ante grade portal vein flow. The celiac axis is then selected and an angiogram is performed. A microcatheter is advanced coaxially through a diagnostic catheter for super selective arteriography of the hepatic arterial branches. The catheter and guidewire are used to select the proper hepatic artery and a limited angiogram performed to identify the branches of the hepatic artery. The right or left hepatic artery is selected distal to the cystic artery (if visualized), depending on the location of the lesions to be treated.

Once the vascular supply of the tumor is identified, chemoembolization of the supplying artery may be performed. At the discretion of the interventional radiologist, extra hepatic vessels may be prophylactically embolized in order to mitigate risk of non-target deposition of LC or ONCOZENE beads, loaded with Irinotecan. Subjects with unifocal tumors will be treated with super-selective chemoembolization. At the discretion of the investigator, a micro catheter may be used to select a second or third-order branch of the right or left hepatic artery in close proximity to the tumor. For multifocal disease or tumor spanning both lobes, a separate chemoembolization procedure will be performed for each lobe. These treatments will be performed in accordance with the study schedule. (e.g. right lobe chemoembolization performed on Week 1, left lobe

chemoembolization performed on Week 4) The goal is for drug delivery. No additional embolic agent will be given after infusion.

Once the catheter is in place within the artery feeding the tumor, the LC or ONCOZENE beads, loaded with Irinotecan will be delivered into the artery. The objective of the therapy will be to deliver up to 2 mL (1 vial, 100 mg Irinotecan) of 70- 150 µm or 100-300 µm LC beads or 40 µm or 75 µm ONCOZENE beads. Bead selection will be based on the size of the tumor(s) using the following criteria:

- For multi-focal tumors < 2 cm, the 70-150 µm LC beads will be used or the 40 µm ONCOZENE beads will be used for the first treatment.
- For all other tumors, the 100-300 µm LC beads will be used or the 75 µm ONCOZENE beads will be used for the first treatment.
- If however, the 100-300 µm LC beads or the 75 µm ONCOZENE beads cannot deliver at least 75% of the planned dose (because of pre-mature stasis), then this indicates these beads are too large for effective treatment. Therefore, the smaller 70-150 µm LC beads or the 40 µm ONCOZENE beads may be used for subsequent treatments.

Radiological non-ionic contrast (preferably Omnipaque or Visipaque) will be used to guide the injection of beads. The beads will be mixed with contrast (according to the instructions for use) immediately prior to the procedure and injected slowly in aliquots under careful fluoroscopic control. Standard precautions will be used for any subject who is taking Metformin and is receiving contrast media. These precautions include asking subjects to stop taking Metformin prior to the administration of the contrast and for 48 hours after the administration of the contrast media. A creatinine of > 2.3 mg/dl will be an exclusion to contrast administration. Catheter selection will be by operator preference (e.g. the choice of a microcatheter, in case of tortuous, narrow or spastic vessels).

If vasospasm occurs, vasodilators may be given at the investigator's discretion. If the vasospasm does not resolve, the procedure should be aborted and the subject rescheduled.

The catheter will then be removed and homeostasis achieved by manual compression or closure device.

The amount of contrast agent delivered to the subject during the procedure and dose of irradiation will be recorded as well as the time exposed to fluoroscopic imaging. The vessels embolized will be noted and the amount of embolic agent used will be recorded. All medications used during the procedure will be recorded, including pain management regime.

2.7.4.3 Embolization Endpoint

The aim of the LC and ONCOZENE beads, loaded with Irinotecan embolization procedure will be to deliver the full dose of LC and ONCOZENE beads, loaded with Irinotecan (100 mg Irinotecan). The embolization endpoint will be until forward flow is reduced but avoiding backward flow of embolic agent that could result in embolization of vessels outside the liver. No additional embolic agent should be used to achieve the

embolization endpoint.

2.7.5 Post Treatment

Following the chemoembolization procedure all subjects will be observed for vital signs, femoral access site, pain management and fluid hydration. The procedure for pain management will be at the investigator's discretion.

Blood for other labs, such as CBC or blood chemistries and magnesium, may also be drawn on all subjects prior to discharge or 72 hours post-procedure.

2.7.6 Discharge

Upon discharge from the hospital, subjects will be given a suitable pain management regime based on normal hospital procedure, if needed. Details of the pain management regime will be recorded in the CRF. Written instructions for pain management will be given to subjects according to their clinical need.

2.8 Chemotherapy Cycles

2.8.1 Control Group

Control Group Subjects randomized to the Control Group will receive the standard systemic chemotherapy (Gem-Cis) or (Gem-Carbo) but without the chemoembolization procedures.

If the treating medical oncologist feels that Cisplatin is not recommended for the subject based on performance status or tolerance then Cisplatin can be replaced with Carboplatin on a case by case decision with the Sponsor. The Carboplatin dose will be based on a Target Area Under the Curve of 4 using the Calvert Formula of Total Carboplatin Dose (mg) = Target AUC x (GFR+25). The maximum dose for AUC of 4 is 600 mg.

2.8.2 Treatment Group

Subjects randomized to the Treatment Group will receive the standard systemic chemotherapy (Gem-Cis) or (Gem-Carbo) AND the chemoembolization procedures.

If the treating medical oncologist feels that Cisplatin is not recommended for the subject based on performance status or tolerance then Cisplatin can be replaced with Carboplatin on a case by case decision with the Sponsor. The Carboplatin dose will be based on a Target Area Under the Curve of 4 using the Calvert Formula of Total Carboplatin Dose (mg) = Target AUC x (GFR+25). The maximum dose for AUC of 4 is 600 mg.

2.8.3 Chemotherapy Procedures

The following procedures will be followed for each chemotherapy cycle for BOTH Control and Treatment Group subjects.

2.8.3.1 Pre-Treatment

Prior to each infusion, the following will be completed for all subjects:

- Physical Exam or Nursing Assessment
- Vital signs
- Laboratory Tests (CBC, CMP, magnesium)
- Adverse Event Monitoring and Concomitant Medication monitoring

2.8.3.2 Treatment

The chemotherapy regimen will be given as Gem-Cis or Gem-Carbo standard chemotherapy with the same assessments and supporting care throughout each cycle.

2.8.3.2.1. Supportive Treatment

Supportive (non-protocol) treatment should be given when required, according to subject's condition. Such supporting treatments include, but are not limited to: anti-emetics, hydration, pain relief, transfusions and growth factors.

2.8.3.2.1.1.1. Anti-emetics

All subjects should receive appropriate antiemetic therapy prior to each chemotherapy infusion.

Due to potential drug-drug interactions, the use of aprepitant (Emend) and dexamethasone (Decadron) for antiemetic therapy should be assessed and appropriate substitutes considered for ALL subjects randomized to the Treatment Group and receiving chemoembolizations.

However, if alternative medications are not felt to be adequate for controlling the side effects of chemotherapy, the CAUTIOUS use of these drugs may be clinically warranted. This determination will be based on the treating physician's discretion and should be reflected in the AEs and SAEs for the subject. If these drugs are utilized, the AEs and SAEs for the subject will need to be followed with additional focus looking for any effects of potential drug interactions.

Aprepitant (Emend) and dexamethasone (Decadron) should be dosed in the following fashion:

- Aprepitant 125 -150 mg intravenously with chemotherapy infusion
- Dexamethasone 10-12 mg intravenously with chemotherapy infusion

2.8.3.2.1.2. Hydration requirements

Hydration guidelines may be added at the discretion of the physician to provide adequate Cisplatin or Carboplatin hydration to maintain renal function and urine output. However, the routine practice is to include at least 250 cc of NS before and after Cisplatin or Carboplatin administration.

2.8.3.3 Dose Modifications for Chemotherapy Treatment (Both Groups)

In the event of chemotherapy-related toxicities, the recommended doses are detailed below. These lab values are based on the subject's labs immediately

prior to a chemotherapy infusion.

All toxicities should be graded according to Common Toxicity Criteria Adverse Events (version 4.0).

2.8.3.3.1 Hematologic Toxicity

- If treatment is delayed > 2 weeks due to hematologic toxicity, the subject's active treatment will be discontinued. However, the subject will still be followed for toxicity and response.
- ANC must be ≥ 1500/mm^3 AND platelet count must be ≥ 75,000/µL on Day 1 of each cycle
- Dose reductions, once initiated, will remain permanent for all future cycles
- Omitted Day 8 doses of Cisplatin or gemcitabine will not be made up.

Absolute Neutrophil Count (ANC) ($x10^6$/L)	Platelets ($x10^6$/L)	% Full dose of Cisplatin or Carboplatin	% Full dose of Gemcitabine
≥ 1500	≥ 75,000	100%	100%
500 – 1499	50,000 – 74,999	75%	75%
< 500	< 50,000	0%	0%

2.8.3.3.2 Renal Toxicity (Cisplatin and Carboplatin only)

Creatinine	% Full dose of Cisplatin or Carboplatin
≤1.5 x ULN	100%
≥ 1.5 but ≤ 2 x ULN	50%
≥ 2 x ULN	0%

2.8.3.3.3 Hepatic Impairment

Total Bilirubin(mg/dl)		AST or ALT	% of Full Dose
≤ 1.5	And	<3X Upper Limit Normal	100%
1.5-1.9	Or	≤ ULN	75%
>1.9	Or	>5 ULN	HOLD

2.8.3.3.4 All Other Non-hematologic Toxicity

- Chemotherapy will be held for ≤ 2 weeks until recovery to Grade 1 or baseline (with exception of alopecia).

- If treatment is delayed > 2 weeks due to non-hematologic toxicity, the subject's active treatment will be discontinued. However, the subject will still be followed for toxicity and response.

2.9 Follow-up Period Visits

2.9.1 Long-Term Follow-up Period

Subjects will be followed every 3-4 months for up to one year after discontinuation of active study treatment. The following information will be collected in subjects who have not had progression of disease:

- Physical examination, including vital signs
- Laboratory determinations (CBC, CMP, magnesium, CA19-9)
- Radiological disease assessment

After each CT or MRI, surgical resectability will be assessed to ensure that this treatment option is not withheld to any subject on study.

2.9.2 Progression Free Follow-up Period

Subjects who have completed the one year Long-Term Follow-up period will need to be evaluated every 3-6 months for radiologic disease assessment only until evidence of progression of disease.

2.9.3 Overall Survival Follow-up

Subjects who have evidence of disease progression will be followed for overall survival follow-up by telephone or standard physician follow-ups as per standard of care until death.

2.9.4 Schema – See Attachment C

2.10 End of Active Study Treatment

Treatment in both arms of the study will only discontinue according to the protocol when the subject shows progression (i.e. lack of therapeutic efficacy) unless they fulfill any of the reasons for withdrawal (see Section 4 Study Termination).

Additionally, subjects in the treatment arm who do not require or fail to receive a second or subsequent chemoembolization treatment should not necessarily be withdrawn from the study unless they fulfill any of the reasons for withdrawal.

3 Adverse Events & Safety Monitoring

3.1 Adverse Event Recording and Evaluation

All adverse events (AEs) must be recorded regardless of causal relationship. All AEs must be followed until resolved or until 30 days post last active study treatment.
Anticipated adverse events will be differentiated from unanticipated adverse events. Anticipated events will be defined as the events listed in the LC Bead package insert and the ONCOZENE Microsphere package insert as potential complications and are included in subjects Informed Consents.

All unanticipated adverse events related to the device will be reported to the FDA within 10 working days, as required per IDE regulation guidelines. In addition, all subject deaths occurring within 60 days of the last treatment will be reported to the FDA.

To allow a standardized safety evaluation across centers and studies, assessment of the seriousness, intensity, outcome and causality of the AEs, should be undertaken by the Investigator using the CTCAE v4.0 criteria.

3.1.1 Adverse Event Intensity

The intensity of each AE must be assessed according to the grades defined in the CTCAE v4.0 classifications. Each Grade refers to the severity of the AE. The CTCAE v4.0 displays Grades 1 – 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild AE
Grade 2	Moderate AE
Grade 3	Severe AE
Grade 4	Life threatening or disabling AE
Grade 5	Death related to AE

It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event need not, by definition, be severe.

3.1.2 Adverse Event Treatment

The treatment of each AE must be assessed according to the following classifications:

None	Subject did not receive any treatment for the AE
Began/Changed Concomitant Medication	New medical treatment was required to treat the AE
Hospitalization/Prolonged Hospitalization	Hospitalization or prolonged stay in the hospital was required due to the AE
Other	Any other treatment was required for the AE

3.1.3 Adverse Event Outcome

The outcome of each AE must be assessed according to the following classification:

Completely recovered:	The subject has fully recovered with no observable residual effects
Not yet completely recovered	Improvement in the subject's condition has occurred, but the subject still has some residual effects
Deterioration	The subject's overall condition has worsened
Permanent damage	The AE has resulted in a permanent impairment
Death	The subject died due to the AE
Ongoing	The AE has not resolved
Unknown	The outcome of the AE is not known because the subject did not return for follow-up (lost to follow-up)

3.1.4 Adverse Event Causality

The causality of each AE must be assessed according to the following classification:

- not assessable
- not related
- unlikely
- possible
- probable
- definite

3.2 Reporting of Adverse Events

Serious adverse events will be appropriately reported by the investigator to the local IRB according to local requirements.

4 Study Termination

4.1 Early Stopping of Active Treatment Based on Toxicity

4.1.1 Dose reduction and Early Stopping Based on Toxicity

Notwithstanding the potential benefit of the treatment, if excess toxicity is observed as below, this would provide grounds for treatment modification, dose reduction or stopping the active study treatments earlier than planned.

4.1.2 Dose Limiting Toxicities

Dose limiting toxicities (DLT) will be defined as any Grade 4 toxicity (excluding nausea, vomiting, and recoverable hematologic toxicities) in more than 3 of each 10 subjects enrolled. The treatment portion of the study would be stopped in the event

the device-related toxicity threshold is reached in more than 3 of 10 study subjects.

Any death within 30 days of treatment on the protocol may be considered a DLT and may invoke a temporary hold in the study, while evaluating attribution. In addition, no more than five device-related deaths will be allowed during the trial.

4.2 Subject Withdrawal from Active Study Treatment

Subjects may be withdrawn from the active treatment portion of the study by the investigator or terminate their participation prematurely based on the following:

- Post-consent determination of ineligibility based on safety or eligibility criteria
- Lack of therapeutic efficacy, as evidenced by progression of treated intrahepatic (i.e. lack of therapeutic efficacy that will not benefit from additional treatment with LC or ONCOZENE beads, loaded with Irinotecan)
- Interval down staging of target lesions such that the subject would be an acceptable candidate for curative treatments
- Physician's judgment following an adverse event
- Termination by the Sponsor or a regulatory authority
- Any other reason for withdrawal that the study physician or subject indicates is in the overall best interest of the subject including initiating other oncotherapy

Subjects who withdraw consent prior to receiving any therapy will be withdrawn from the study and no follow-up safety surveillance is required. These will be captured as screen fails on the Enrollment Logs.

Subjects who voluntarily withdraw consent or who are withdrawn by the study physician for any reason after receiving therapy will be followed up for at least 7 days. The purpose of this follow-up is to capture all adverse events and document any serious, procedure related adverse events.

If a subject dies prior to the last scheduled study visit**,** the date and cause of death will be recorded.

4.3 Study Termination

The study will be considered terminated for a subject if:

- Consent has been revoked by the subject, or
- Subject has been deemed Lost to Follow-Up, or
- Upon the subject's death

5 Data Analysis and Statistical Considerations

Fifty-four subjects will be enrolled into the study and randomized to combination therapy or systemic therapy in a 1:1 fashion. This section details the sample size calculation and provides justification for this number of subjects along with the randomization plan.

5.1 Sample Size Calculation

The primary endpoint will be tumor response, as defined by the modified RECIST criteria. Subjects exhibiting complete or partial response will be classified as responders and all other subjects as non-responders. The response rate in the intravenous chemotherapy group can be assumed to be 25%, and we expect to see response rates of 70% in the

chemoembolization with LC and ONCOZENE beads loaded with Irinotecan group. The sample size of 54 subjects provides 80% power for a Fisher's exact test to detect the given difference between the assumed proportions at a significance level of 0.05.

5.2 Randomization

The 54 subjects will be randomized in a 1:1 ratio to receive either combination therapy or systemic therapy alone. A randomized list using an envelope lottery method will be generated by the Sponsor. The lottery numbers will be assigned by the Sponsor and administered by the Sponsor's Study Coordinators. She/he will be the only person(s) with access to the lottery assignments if the need arises for review. This lottery style envelope will be locked and will not be viewed by any of the treating personnel. Subjects will receive either combination therapy or systemic therapy alone based on the randomization via the sealed opaque envelope method. This is an acceptable way to ensure that subject assignment is not predictable and leads to complete randomization. The principal investigator, all investigators, as well as other research personnel, will not be aware of the starting point once the randomized portion of the study is commenced.

One master envelope containing 54 sealed individual envelopes will be created at the beginning of the randomized part of this study and will be randomly given to the study coordinator to be opened after a subject has been consented to the study.

5.3 Populations for Analysis

The As Treated population will include all randomized subjects who receive at least one cycle of intravenous chemotherapy or LC or ONCOZENE beads loaded with Irinotecan. Subjects will be included in the As Treated Population according to treatment actually received.

The Intention-to-treat (ITT) population will include all randomized subjects who receive at least one cycle of intravenous chemotherapy or LC or ONCOZENE beads loaded with Irinotecan. All subjects will be grouped according to their randomization regardless of treatment received.

The Modified intention-to-treat (MITT) population will include all randomized subjects who receive at least one cycle of intravenous chemotherapy (control group) or at least one chemoembolization treatment with LC or ONCOZENE beads loaded with Irinotecan (test group) and whose progression free survival is evaluable.

The Per-protocol (PP) population will include all subjects who receive at least one intravenous chemotherapy cycle (control group) or at least one chemoembolization treatment with LC or ONCOZENE beads loaded with Irinotecan in combination with intravenous chemotherapy (test group) and who were treated according to their randomization schedule. Subjects with major protocol deviations or who did not receive treatment according to their randomization schedule will be excluded from the PP population.

5.3.1 Subject Demographics/Other Baseline Characteristics

The following demographic and baseline characteristics will be summarized descriptively by treatment group:

- Gender and age
- ECOG performance status

- Bilobar disease
- Tumor marker (CA19-9)
- Disease status
- Other characteristics (e.g. liver chemistry)

Medical history will be coded and summarized by primary body system organ class and preferred term.

5.3.2 Treatments (study treatments and concomitant medications)

The number and dose of intravenous chemotherapy cycles and the number of chemoembolization treatments and dose of LC or ONCOZENE beads, loaded with Irinotecan will be summarized by treatment group.

5.4 Efficacy Analysis

5.4.1 Primary Endpoint

All safety parameters will be analyzed descriptively based on the As Treated population and reported in an interim report to FDA The primary objective of the study is to test the superiority of transarterial chemoembolization using LC or ONCOZENE beads loaded with Irinotecan in combination with first line chemotherapy (test group) compared with first line chemotherapy alone (control group) in terms of tumor response. Any subjects that withdraw before study end will be censored at that point.

The hypotheses to be tested for this primary efficacy endpoint are as follows:

- H_0: Tumor response under chemotherapy and chemoembolization is the same as that under chemotherapy alone ($S_{test}(t) = S_{control}(t)$)
- H_A: Tumor response under chemotherapy and chemoembolization is better than that under chemotherapy alone ($S_{test}(t) > S_{control}(t)$)

The primary efficacy analysis will be performed on the MITT population. For sensitivity reasons, the primary efficacy analysis will also be carried out for both ITT and PP populations.

In general, missing data will not be replaced, if not absolutely indicated.

5.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints will be the following variables:

- Local Tumor Response (extent of necrosis in the treated lesions)
- Time to Progression
- Hepatic Progression Free Survival
- Change in tumor markers
- Overall survival
- Patient Tolerance

Categorical variables will be summarized using frequency tables and Fisher's exact test will be used to compare the treatment groups. Multivariate analyses and logistic regression will be applied to adjust the influences of center and other prognostic factors, if appropriate.

For time-to-event variables, the Kaplan-Meier method will be used to estimate the event free survival, and the log-rank test will be conducted to compare the two treatment groups. Multivariate analysis and Cox's proportional hazard model will be used to adjust for the influences of center and other prognostic factors, if appropriate.

For continuous variables, descriptive statistics will be provided and Student's t tests will be used to compare treatment groups. A linear mixed model will be employed to compare the two treatment groups: with treatment, time (if applicable), center and other prognostic factors as fixed effects, time-window as a repeated factor (if applicable), and subjects as a random factor.

All secondary efficacy analyses will be based on the ITT population and the corresponding statistical testing results will be interpreted in the exploratory sense.

6 Ethical and Legal Considerations

6.1 Informed Consent Procedures

Subject's informed consent will be obtained and documented according to the principles of informed consent in the current version of the 21CFR50 (Protection of Human Subjects), Declaration of Helsinki (2008) and the International Conference on Harmonization Guideline for Good Clinical Practice (ICH-GCP).

Prior to obtaining informed consent, subjects will be given a full explanation, in lay terms, of the study purpose and procedures related to the study. The risks and benefits of the procedures will be explained to the subject. The palliative role of chemoembolization should be clearly understood by both the subject and his/her family (if appropriate). Subjects should also be informed about post-embolization syndrome (PES) that may be experienced in over 60% of cases, as well as other treatment-related complications. Post embolization syndrome often includes pain, fever, nausea and vomiting that can last from a few hours to a few days. Subjects will be informed of the potential risk of treatment related death.

It will be explained that they may refuse to take part in, or withdraw from the study without prejudice to their future care and treatment. Subjects should not be coerced, persuaded, or unduly influenced to participate or remain in the trial. A subject must be given ample time and opportunity to inquire about details of the trial and all questions about the trial should be answered to the satisfaction of the subject.

Written informed consent will be obtained from all subjects prior to entry into the study. The written informed consent document must be IRB-approved and must be signed and personally dated by the subject. If the subject is unable to read the consent form, a witness should be present during the entire informed consent discussion. The subject will be given a copy of his/her signed informed consent document.

6.2 Notification/Submission to Regulatory Authority(ies)

The investigator will assure that an appropriately constituted Institutional Review Board (IRB) complies with the requirements of the International Conference on Harmonization Guidelines. Prior to initiation of the study, the investigator will forward copies of the protocol, informed consent form and all other appendices to be used for the study to the IRB for its review and approval. A copy of the approval from the IRB plus other regulatory documents must be forwarded to the sponsor or their designee, before any

investigational supplies can be shipped to the investigator.

6.3 Local Regulations and Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformance with US Title 21CFR50 (Protection of Human Subjects), the principles of the "Declaration of Helsinki" (as amended in Japan, Italy, Hong Kong, South Africa, Scotland, USA and Japan (2008) or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to all applicable local regulatory requirements, inclusive of US Title 21CFR812 (Investigational Device Exemptions).

6.4 Subject Privacy / Confidentiality

All data generated from this study will remain confidential and no published report will contain any reference to subject names or identifying features. The investigator will assure that subjects protected health information will be securely maintained protected from unauthorized parties.

6.5 Monitoring Procedures

The trial will be monitored to verify that the rights and well-being of subjects are protected, that the reported trial data are accurate, complete and verifiable from source documents and that the conduct of the study complies with the current approved protocol/amendments(s), with Good Clinical Practice, and with the applicable laws and/or regulations.

The Sponsor or its designee will be responsible for monitoring the trial according to their SOPs, GCP and applicable regulations in order to ensure that investigator recruitment, and study initiation, execution and closure are adequate.

It is understood that the responsible monitor (or designee) will contact and visit the investigator regularly and will be allowed, on request, to inspect the various records of the trial (Case Report Forms and other pertinent data) provided that subject confidentiality is maintained in accord with local requirements. As such, the investigator and their staff will be expected to cooperate with the Sponsor or its designee and to be available during at least a portion of the monitoring visits to answer questions and to provide any missing information.

It will be the monitor's responsibility to inspect the Case Report Forms (CRF) at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The monitor should have access to laboratory test reports and other subject records needed to verify the entries on the Case Report Form. The investigator (or his/her deputy) agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

Data monitoring will be conducted by designated monitoring personnel at University of Louisville, School of Medicine Department of Surgery.

6.6 Source Data Verification

Source data verification (SDV) is an essential element to ensure accuracy and credibility of the data, and conclusions derived from clinical investigations. Source data verification will normally be conducted in conjunction with data monitoring. Entries in the Case

Report Forms (CRF) will be verified using the original documents such as subject files, informed consent forms signed by subjects, device/drug accountability forms, and hospital medical records.

Investigational sites shall supply the Sponsor or its designee on request with any required background data from the study documentation or clinic records. This is particularly important when Case Report Forms are illegible or when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

Investigators and/or Research coordinators at the clinical site will perform primary data collection based on source-documented hospital chart reviews. University of Louisville Department of Surgery will provide clinical monitoring on behalf of the Sponsor, including review of CRFs and parity checks with the source documentation including operator work sheets retained with CRF documentation and hospital charts.

6.7 Study Quality Assurance

The Sponsor has designated Office of Clinical Research Services and Support (OCRSS – the Central Clinical Trials Office at the University of Louisville) to act as the QAU for this IDE application. The QAU will provide assurance to the Sponsor that all regulatory requirements have been met related to the submission of the IDE and related documents. The monitoring of the trial conduct will be handled as discussed in the monitoring section above.

7 IRB Information

The following IRBs will review and approve the research related to this IDE:

Human Subjects Protection Program
University of Louisville Institutional Review Board
Med Center One, Suite 200
University of Louisville
501 E. Broadway
Louisville, Kentucky 40202
Phone: (502) 852-5188
Fax: (502) 852-2164
Chairperson: Laura Clark, MD

8 Investigator Agreements

8.1 Certification of Investigator Agreement

The sponsor certifies that:

All the investigators who participate in the investigation have signed an Investigator Agreement.

The list of investigators provided in the previous section includes all the investigators participating in the clinical investigation of the device.

No investigators will be added to the clinical investigation of the device until they have signed an Investigator Agreement.

9 Reference List

1. Aljiffry M, Walsh MJ, Molinari M. Advances in diagnosis, treatment and palliation of cholangiocarcinoma: 1990-2009. World J Gastroenterol 2009;15:4240-62.

2. Shaib YH, El-Serag HB, Davila JA, Morgan R, McGlynn KA. Risk factors of intrahepatic cholangiocarcinoma in the United States: a case-control study. Gastroenterology 2005;128:620-6.

3. Choi CW, Choi IK, Seo JH, Kim BS, Kim JS, Kim CD, Um SH, Kim YH. Effects of 5-fluorouracil and leucovorin in the treatment of pancreatic-biliary tract adenocarcinomas. Am J Clin Oncol 2000;23:425-8.

4. Rocha FG, Matsuo K, Blumgart LH, Jarnagin WR. Hilar cholangiocarcinoma: the Memorial Sloan-Kettering Cancer Center experience. J Hepatobiliary Pancreat Sci 2009;17:490-6.

5. Jarnagin WR, Fong Y, DeMatteo RP, Gonen M, Burke EC, Bodniewicz BJ, Youssef BM, Klimstra D, Blumgart LH. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg 2001;234:507-17; discussion 17-9.

6. Yang J, Yan LN. Current status of intrahepatic cholangiocarcinoma. World J Gastroenterol 2008;14:6289-97.

7. Vauthey JN, Blumgart LH. Recent advances in the management of cholangiocarcinomas. Semin Liver Dis 1994;14:109-14.

8. Endo I, Gonen M, Yopp AC, Dalal KM, Zhou Q, Klimstra D, D'Angelica M, DeMatteo RP, Fong Y, Schwartz L, Kemeny N, O'Reilly E, Abou-Alfa GK, Shimada H, Blumgart LH, Jarnagin WR. Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. Ann Surg 2008;248:84-96.

9. Eckel F, Schmid RM. Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. Br J Cancer 2007;96:896-902.

10. Saxena A, Bester L, Chua TC, Chu FC, Morris DL. Yttrium-90 radiotherapy for unresectable intrahepatic cholangiocarcinoma: a preliminary assessment of this novel treatment option. Ann Surg Oncol 2009;17:484-91.

11. Sanz-Altamira PM, O'Reilly E, Stuart KE, Raeburn L, Steger C, Kemeny NE, Saltz LB. A phase II trial of irinotecan (CPT-11) for unresectable biliary tree carcinoma. Ann Oncol 2001;12:501-4.

12. Ducreux M, Van Cutsem E, Van Laethem JL, Gress TM, Jeziorski K, Rougier P, Wagener T, Anak O, Baron B, Nordlinger B. A randomised phase II trial of weekly high-dose 5-fluorouracil with and without folinic acid and cisplatin in patients with advanced biliary tract carcinoma: results of the 40955 EORTC trial. Eur J Cancer 2005;41:398-403.

13. Kim MJ, Oh DY, Lee SH, Kim DW, Im SA, Kim TY, Heo DS, Bang YJ. Gemcitabine-based versus fluoropyrimidine-based chemotherapy with or without platinum in unresectable biliary tract cancer: a retrospective study. BMC Cancer 2008;8:374.

14. Rao S, Cunningham D, Hawkins RE, Hill ME, Smith D, Daniel F, Ross PJ, Oates J, Norman AR. Phase III study of 5FU, etoposide and leucovorin (FELV) compared to epirubicin, cisplatin and 5FU (ECF) in previously untreated patients with advanced biliary cancer. Br J Cancer 2005;92:1650-4.

15. Knox JJ, Hedley D, Oza A, Feld R, Siu LL, Chen E, Nematollahi M, Pond GR, Zhang J, Moore MJ. Combining gemcitabine and capecitabine in patients with advanced biliary cancer: a phase II trial. J Clin Oncol 2005;23:2332-8.

16. Knox JJ, Hedley D, Oza A, Siu LL, Pond GR, Moore MJ. Gemcitabine concurrent with continuous infusional 5-fluorouracil in advanced biliary cancers: a review of the Princess Margaret Hospital experience. Ann Oncol 2004;15:770-4.

17. Thongprasert S, Napapan S, Charoentum C, Moonprakan S. Phase II study of gemcitabine and cisplatin as first-line chemotherapy in inoperable biliary tract carcinoma. Ann Oncol 2005;16:279-81.

18. Lee GW, Kang JH, Kim HG, Lee JS, Jang JS. Combination chemotherapy with gemcitabine and cisplatin as first-line treatment for immunohistochemically proven cholangiocarcinoma. Am J Clin Oncol 2006;29:127-31.

19. Kim ST, Park JO, Lee J, Lee KT, Lee JK, Choi SH, Heo JS, Park YS, Kang WK, Park K. A Phase II study of gemcitabine and cisplatin in advanced biliary tract cancer. Cancer 2006;106:1339-46.

20. Valle JW, Wasan H, Johnson P, Jones E, Dixon L, Swindell R, Baka S, Maraveyas A, Corrie P, Falk S, Gollins S, Lofts F, Evans L, Meyer T, Anthoney A, Iveson T, Highley M, Osborne R, Bridgewater J. Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: a multicentre randomised phase II study - The UK ABC-01 Study. Br J Cancer 2009;101:621-7.

21. Civalleri D, Esposito M, Fulco RA, Vannozzi M, Balletto N, DeCian F, Percivale PL, Merlo F. Liver and tumor uptake and plasma pharmacokinetic of arterial cisplatin administered with and without starch microspheres in patients with liver metastases. Cancer 1991;68:988-94.

22. Soulen MC. Chemoembolization of hepatic malignancies. Oncology (Williston Park) 1994;8:77-84; discussion , 9-90 passim.

23. Kameyama M, Imaoka S, Fukuda I, Nakamori S, Sasaki Y, Fujita M, Hasegawa Y, Iwanaga T. Delayed washout of intratumor blood flow is associated with good response to intraarterial chemoembolization for liver metastasis of colorectal cancer. Surgery 1993;114:97-101.

24. Kato T, Nemoto R, Mori H, Takahashi M, Harada M. Arterial chemoembolization with mitomycin C microcapsules in the treatment of primary or secondary carcinoma of the kidney, liver, bone and intrapelvic organs. Cancer 1981;48:674-80.

25. Kato T, Nemoto R, Mori H, Takahashi M, Tamakawa Y, Harada M. Arterial chemoembolization with microencapsulated anticancer drug. An approach to selective cancer chemotherapy with sustained effects. JAMA 1981;245:1123-7.

26. Fujimoto S, Miyazaki M, Endoh F, Takahashi O, Okui K, Morimoto Y. Biodegradable mitomycin C microspheres given intra-arterially for inoperable

hepatic cancer. With particular reference to a comparison with continuous infusion of mitomycin C and 5-fluorouracil. Cancer 1985;56:2404-10.

27. Cantore M, Mambrini A, Fiorentini G, Rabbi C, Zamagni D, Caudana R, Pennucci C, Sanguinetti F, Lombardi M, Nicoli N. Phase II study of hepatic intraarterial epirubicin and cisplatin, with systemic 5-fluorouracil in patients with unresectable biliary tract tumors. Cancer 2005;103:1402-7.

28. Kemeny NE, Ron IG. Liver Metastases. Curr Treat Options Gastroenterol 1999;2:49-57.

29. Nott DM, Yates J, Grime SJ, Maltby M, Cooke TG, Jenkins SA. The effect of portal venous flow on the washout of a regionally injected marker substance 99mTc-methylene diphosphonate after hepatic arterial blockade with degradable starch microspheres. Eur J Surg Oncol 1992;18:347-52.

30. Pentecost MJ. Transcatheter treatment of hepatic metastases. AJR Am J Roentgenol 1993;160:1171-5.

31. Geoghegan JG, Scheele J. Treatment of colorectal liver metastases. Br J Surg 1999;86:158-69.

32. Patel NH, Jindal RM. The role of chemoembolization in the treatment of colorectal hepatic metastases. Hepatogastroenterology 2001;48:448-52.

33. You YT, Changchien CR, Huang JS, Ng KK. Combining systemic chemotherapy with chemoembolization in the treatment of unresectable hepatic metastases from colorectal cancer. Int J Colorectal Dis 2006;21:33-7.

34. Abramson RG, Rosen MP, Perry LJ, Brophy DP, Raeburn SL, Stuart KE. Cost-effectiveness of hepatic arterial chemoembolization for colorectal liver metastases refractory to systemic chemotherapy. Radiology 2000;216:485-91.

35. Urego M, Flickinger JC, Carr BI. Radiotherapy and multimodality management of cholangiocarcinoma. Int J Radiat Oncol Biol Phys 1999;44:121-6.

36. Goldstein RM, Stone M, Tillery GW, Senzer N, Levy M, Husberg BS, Gonwa T, Klintmalm G. Is liver transplantation indicated for cholangiocarcinoma? Am J Surg 1993;166:768-71; discussion 71-2.

37. Malagari K. Drug-eluting particles in the treatment of HCC: chemoembolization with doxorubicin-loaded DC Bead. Expert Rev Anticancer Ther 2008;8:1643-50.

38. Fiorentini G, Aliberti C, Turrisi G, Del Conte A, Rossi S, Benea G, Giovanis P. Intraarterial hepatic chemoembolization of liver metastases from colorectal cancer adopting irinotecan-eluting beads: results of a phase II clinical study. In Vivo 2007;21:1085-91.

39. de Forni M, Bugat R, Chabot GG, Culine S, Extra JM, Gouyette A, Madelaine I, Marty ME, Mathieu-Boue A. Phase I and pharmacokinetic study of the camptothecin derivative irinotecan, administered on a weekly schedule in cancer patients. Cancer Res 1994;54:4347-54.

40. Martin RC, Robbins K, Tomalty D, O'Hara R, Bosnjakovic P, Padr R, Rocek M, Slauf F, Scupchenko A, Tatum C. Transarterial chemoembolisation (TACE) using irinotecan-loaded beads for the treatment of unresectable metastases to the liver in

patients with colorectal cancer: an interim report. World J Surg Oncol 2009;7:80.

41. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205-16.

42. Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, Sherman M, Schwartz M, Lotze M, Talwalkar J, Gores GJ. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst 2008;100:698-711.

Attachment A - Protocol Schema

Study Schema - Control Subject												
Week Number	0	1	2	3	4	5	6	7	8	9†	LT-FU	S-FU
	Baseline/ Screening	Active Treatment									q 3-4 months‡	q 3-4 months≠
		Cycle 1			Cycle 2			Cycle 3				
Gem-Cis/Gem-Carbo Chemotherapy		x	x		x	x		x	x			
Inclusion/Exclusion	x											
Informed consent	x											
Demographics	x											
Medical / Surgical History	x											
Physical Exam/Nursing Assessment	x	x	x		x	x		x	x	x	x	
Vital signs	x	x	x		x	x		x	x	x	x	
CBC, CMP	x	x	x		x	x		x	x	x	x	
Coagulation	x	*	*	*	*	*	*	*	*	*	*	
Tumor markers	x									x	x	
Magnesium		x	x		x	x		x	x	x		
CT chest	x											
3 phase CT/MRI abd. and pelvis	x									x	x∞	
AE Monitoring	x	x	x	x	x	x		x	x	x	x#	
Concomitant medications	x	x	x	x	x	x		x	x	x	x#	
Telephone / S.O.C. Physician Visits												x
*if clinically indicated												
†Additional active treatment in 3 Cycle increments												
‡Upon completion of Active Treatment w/o P.O.D.												
∞If no P.O.D. upon completing 1 year of LT-FU, only radiological FU is continued												
#Followed up to 30 days post last active study treatment												
≠Completed upon evidence of P.O.D. until Death												

Study Schema - Treatment Subject													
Week Number	0	1	2	3	4	5	6	7	8	9	10†	LT-FU	S-FU
	Baseline Screening	Active Treatment										q 3-4 months‡	q 3-4 months≠
			Cycle 1			Cycle 2			Cycle 3				
Chemoembolization		x			x			x*					
Gem-Cis/Gem-Carbo Chemotherapy			x	x		x	x		x	x			
Inclusion/Exclusion	x												
Informed consent	x												
Demographics	x												
Medical / Surgical History	x												
Physical Exam/Nursing	x	x	x	x	x	x	x	x	x	x	x	x	
Vital signs	x	x	x	x	x	x	x	x	x	x	x	x	
CBC, CMP	x	x	x	x	x	x	x	x	x	x	x	x	
Coagulation	x	*	*	*	*	*	*	*	*	*	*	*	
Tumor markers	x										x	x	
Magnesium		x	x	x	x	x	x	x	x	x	x		
CT chest	x												
3 phase CT/MRI abd. and pelvis	x										x	x∞	
AE Monitoring	x	x	x	x	x	x	x	x	x	x	x	x#	
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x#	
Telephone / S.O.C. Physician Visits													x

*if clinically indicated

†Additional active treatment in 3 Cycle increments

‡Upon completion of Active Treatment w/o P.O.D.

∞If no P.O.D. upon completing 1 year of LT-FU, only radiological FU is continued

#Followed up to 30 days post last active study treatment

≠Completed upon evidence of P.O.D. until Death

Attachment B
Study Treatment Plan

CONTROL GROUP

The **Control Group** will receive Gem/Cis or Gem/Carbo chemotherapy at the following time points:

Week 1: Chemo Cycle 1 (Day 1)

Week 2: Chemo Cycle 1 (Day 8)

Week 3: REST

Week 4: Chemo Cycle 2 (Day 1)

Week 5: Chemo Cycle 2 (Day 8)

Week 6: REST

Week 7: Chemo Cycle 3 (Day 1)

Week 8: Chemo Cycle 3 (Day 8)

Week 9: CT or MRI and office visit to evaluate response to therapy. This schedule of treatments will continue based on subject's tolerance and response to therapy.

TEST GROUP

The **Test Group** will receive LC or ONCOZENE beads chemoembolizations and Gem/Cis or Gem/Carbo chemotherapy at the following time points:

Week 1: Bead Treatment

Week 2: Chemo Cycle 1 (Day 1)

Week 3: Chemo Cycle 1 (Day 8)

Week 4: Bead Treatment

Week 5: Chemo Cycle 2 (Day 1)

Week 6: Chemo Cycle 2 (Day 8)

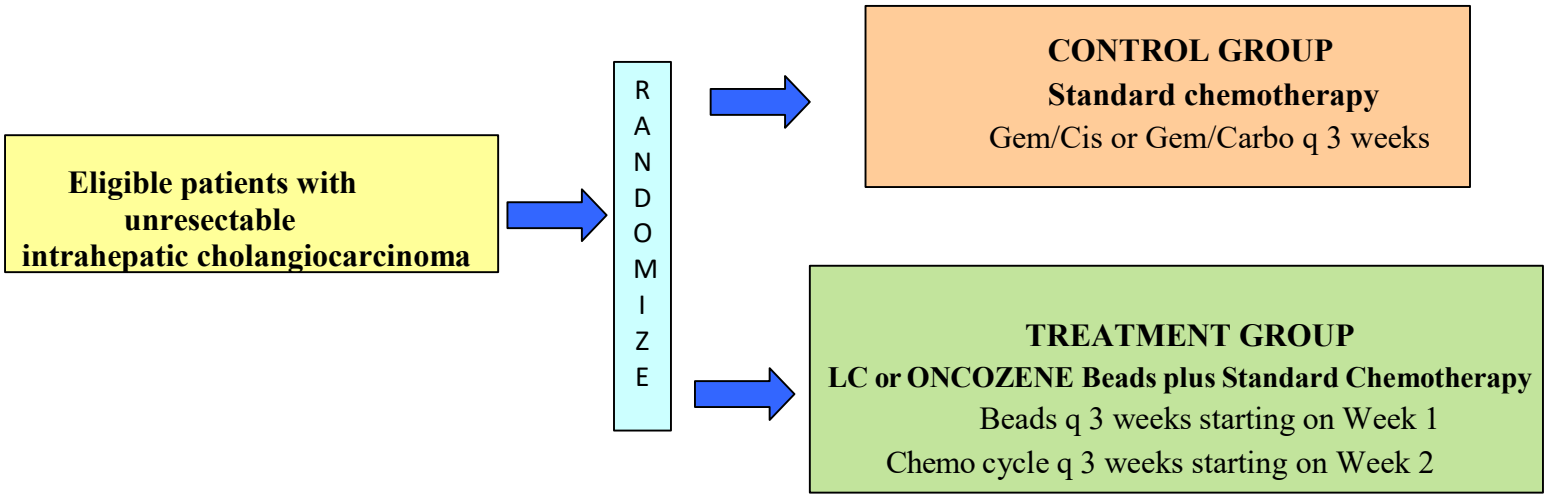
Week 7: Bead Treatment

Week 8: Chemo Cycle 3 (Day 1)

Week 9: Chemo Cycle 3 (Day 8)

Week 10: CT or MRI and office visit to evaluate response to therapy. This schedule of treatments will continue based on subject's tolerance and response to therapy.

Attachment C - Study Treatment Plan



CONTROL GROUP:

Standard chemotherapy consisting of Gemcitabine / Cisplatin or Gemcitabine / Carboplatin*

Each chemotherapy cycle is 21 days consisting of Gem/Cis or Gem/Carbo infusions on Day 1 and Gem/Cis or Gem alone on Day 8 and 1 week of rest following. (There is a +/- 3 day window on all chemotherapy treatments.)

- Cisplatin at 25 mg/m^2 given as a 2-hour IV infusion on Days 1 and 8.
- Or, Carboplatin given as a 2-hour IV infusion on **Day 1 only**. Carboplatin dose (mg) = (target AUC) x (GFR + 25) with a target AUC of 4.The max dose for AUC of 4 is 600 mg.
- And, Gemcitabine at 1000 mg/m^2 given as a 30-minute IV infusion after Cisplatin or Carboplatin on Day 1 and after Cisplatin on Day 8.

OR

TEST GROUP:

Chemoembolization with Irinotecan loaded-LC or ONCOZENE beads plus standard chemotherapy consisting of Gemcitabine / Cisplatin or Gemcitabine / Carboplatin.*

- Chemoembolization with Irinotecan loaded-LC or ONCOZENE beads performed q 3 weeks, starting on Week 1** (There is a +/- 3 day window on all chemoembolization treatments.)

First chemotherapy treatment will occur one week after the first chemoembolization procedure which occurs at Week 2 on the study calendar. Each chemotherapy cycle is 21 days, consisting of Gem/Cis or Gem/Carbo infusions on Days 1 and Gem/Cis or Gemzar alone on Days 8 and 1 week of rest following. (There is a +/- 3 day window on all chemotherapy treatments.)

- Cisplatin at 25 mg/m^2 given as a 2-hour IV infusion on Days 1 and 8, starting on Week 2.**
- Or, Carboplatin given as a 2-hour IV infusion on **Day 1 only** starting on Week 2. Carboplatin dose (mg) = (target AUC) x (GFR + 25) with a target AUC of 4. The max dose for AUC of 4 is 600 mg.
- And, Gemcitabine at 1000 mg/m^2 given as a 30-minute IV infusion after Cisplatin or Carboplatin on Day 1 and after Cisplatin on Day 8.

*All treatment regimens will be given until progression of disease or until the treating physician determines it is in subject's best interest to discontinue therapy.

**Subjects in the TEST GROUP may receive additional chemoembolization treatments, up to a maximum number of 6 treatments, if the investigator believes this in subject's best interest, based on subject's response and tolerance to treatment and subject's overall burden of disease.